RANDOM WALK MODEL BASED ON DTI FOR PREDICTING THE MICROSCOPIC SPREAD OF GLIOMAS

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ABSTRACT

The current methods of determining the treatment margins for Stereotactic Radiotherapy (SRT) are often inadequate as recurrences and/or secondary tumors occur at/near the boundaries of the treatment margin. If our hypothesis that paths of elevated water diffusion provide a preferred route for migration of cancer cells is correct then future SRT treatment volumes would be modified to provide elongated margins along the paths of elevated water diffusion; thereby reducing the incidence of recurrence. We hypothesize that the migration of tumor cells from the surface of the tumor can be predicted using a random walk model constrained by the local diffusion environment. In our implementation the diffusion environment is represented by the Principal Diffusion Direction (PDD) obtained from Diffusion Tensor Imaging (DTI). The results based on the analysis of DTI datasets of patients who had recurrences show a high correlation between areas of high cell concentration determined using the random walk model and the location of recurrences and/or secondary tumors.

Index Terms— Diffusion Tensor Imaging, Gliomas, Stereotactic Radiotherapy, Treatment margin

1. INTRODUCTION

Each year in the United States approximately 17,000 new cases of primary bain tumor are diagnosed [1]. Some of the common primary brain tumors are glioblastomas and astrocytomas. For glioblastomas, with current chemotherapy and radiation techniques the 5-year survival rate for patients over 45 is less than 2% and the local control rate is only 9% [2].

A typical Stereotactic Radiotherapy (SRT) treatment plan for a high-grade glioma includes a uniform margin of up-to 25mm surrounding the lesion to account for any unobserved microscopic spread of tumor cells. This isotropic margin unfortunately leads to the unnecessary ablation of healthy tissue in certain directions resulting in cognitive dysfunction, while in certain directions the margin is too small leading to distant tumor recurrences. The goal of this study is to use magnetic resonance (MR) Diffusion Tensor Imaging (DTI) to predict microscopic tumor spread of aggressive brain tumors and to help us better understand the mechanism of tumor spread. These enhancements could lead to improved anisotropic margins for radiation treatment of malignant brain tumors that would achieve greater local cancer control and increased patient survival while decreasing harmful side-effects currently associated with radiation therapy.

Our scientific hypothesis is that migrating brain cancer cells follow the paths of least resistance and this migration of tumor cells from the tumor surface can be predicted using a random walk model constrained by the local diffusion environment as determined from MR DTI. In areas of white matter the direction of greatest diffusion usually parallels the predominant underlying fiber orientation and it is known from postmortem studies in humans that glioma cancer cells that migrate the greatest distance from the primary tumor site are located predominantly along white matter tracts [3]. Jacobsen et al. observed that during embryogenesis neonatal astrocytes show a preferential movement along developing axon tracts [4]. Thus these glioma cells have an inherent tendency to move along white matter tracts.

The local anisotropic diffusion of water molecules in the brain can be measured non-invasively in-vivo using MR DTI [5]. The local 3D diffusion environment is expressed by the diffusion tensor and the process of computing the diffusion tensor at each voxel in the image is called DTI.

2. METHODS AND MATERIALS

2.1. Image Acquisition

DTI datasets were acquired for patients who were treated for aggressive glioma with SRT at the University of Rochester Medical Center. Acquisition of the DTI data was performed at the earliest time point possible to obtain a measurement of the diffusion environment that is least altered by the tumor. The datasets were obtained prior to surgical resection of tumor and SRT or after surgical resection but before SRT.

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The DTI dataset at the time point with minimum edema was used. The analysis was performed either retrospectively or prospectively. For the retrospective study the DTI datasets were acquired using a clinical whole body 1.5T scanner (General Electric - SIGNA EXCITE) as part of the standard of care imaging protocol. DTI was performed using one of the following EPI sequences using the following parameters: 1) TR 10s; TE 89.4 ms; 22-26 serial axial slices; 25 diffusion gradient directions and 3 reference (b=0) scans; and voxel dimensions of $0.98 \times 0.98 \times 6$ mm or 2) TR 10.8s; TE 101.3ms, 38 axial slices; 21 diffusion encoding directions and 2 reference scans and voxel dimensions of $0.94 \times 0.94 \times 3$ mm. For the prospective study, DTI was performed using an EPI sequence on a 3.0T Siemens scanner with 70 serial axial slices of voxel dimensions $2.0 \times 2.0 \times 2.0$ mm; TR 10.1s; TE 100 ms; 60 diffusion gradient directions and 10 reference scans.

2.2. DTI Reconstruction

For the retrospective study the DTI datasets were reconstructed using DTIStudio [6], a streamline tractogaphy tool made available by Mori et al. . The Diffusion Tensor (DT) was diagonalized and the eigen values and vectors were calculated by DTIStudio. The Principal Diffusion Direction (PDD) which is the eigen vector corresponding to the largest eigen value was exported as a raw file and the Fractional Anisotropy (FA), which is a measure of directionality, was exported as an analyze image. For the prospective study the DTI datasets were reconstructed using Camino [7], a tool for analysis and reconstruction of Diffusion MRI data made available by Alexander et al. . The DTI datasets were available as mosaic images and were converted to SPM analyze format using MRIConvert[1]. The diffusion data was reconstructed using a single tensor model with Camino, the DT was diagonalized and the eigen system was obtained. The FA was obtained as an analyze image and the PDD as a raw file.

2.3. Random Walk Model

The assumptions of our random walk model are: 1) Initially there are an equal number of cells in all surface voxels of the tumor; 2) The initial cell concentration is a step function with all cells in the surface voxels and 3) The migration is constrained by the PDD. The tumor mask was generated manually using FSLView, the brain mask was generated using FSL [8] and the ventricles were segmented using an in-house software based on thresholding and flood-fill. The algorithm of our random walk model is given below. In the algorithm $c2s$ is the function to convert from cartesian to spherical coordinate system; $s2c$ is the function to convert from spherical to cartesian coordinate system; d is the function to calculate the euclidean distance between two points, rand[-1,1] is a random number between -1 and 1, δ is the step size expressed as a fraction of the in-plane resolution and $[\Phi, \Theta, r]$ are PDDs spherical coordinates with origin at the center of the voxel.

Input: PDD, FA, brain mask, tumor mask, ventricle mask.
Output: for each voxel a count of how many different cancer cells visited it.
$ct :=$ center of tumor.
foreach *surface voxel* v **do**
  initialize cell concentration for v to 500.
  $pos :=$ center of v.
  foreach *cell* c *in* v **do**
    $[\Phi, \Theta, r] := c2s(PDD[v])$
    $$max\Delta Angle := \begin{cases} 35^\circ & \text{if } FA[v] < 0.3 \\ 10^\circ & \text{if } FA[v] > 0.6 \\ 20^\circ & \text{otherwise} \end{cases}$$
    $$\delta := \begin{cases} 0.15 & \text{if } FA[v] < 0.3 \\ 0.4 & \text{if } FA[v] > 0.6 \\ 0.25 & \text{otherwise} \end{cases}$$
    $new\Theta := \Theta + max\Delta Angle \cdot rand[-1, 1]$
    $new\Phi := \Phi + max\Delta Angle \cdot rand[-1, 1]$
    $p1 := pos + s2c(new\Theta, new\Phi, r) \cdot \delta$
    $p2 := pos - s2c(new\Theta, new\Phi, r) \cdot \delta$
    switch *based on regions of* $p1$ *and* $p2$ **do**
      case $p1$ *and* $p2$ *inside the tumor or while voxel with* $FA > 0.5$ *not visited*
        $$pos := \begin{cases} p1 & \text{if } d(p1, ct) > d(p2, ct) \\ p2 & \text{otherwise} \end{cases}$$
      end
      case $p1$ *and* $p2$ *inside the brain but one in tumor and other outside*
        $pos :=$ the point not in the tumor
      end
      case *both outside the tumor*
        $$pos := \begin{cases} p1 & \text{if } d(p1, pos) > d(p2, pos) \\ p2 & \text{otherwise} \end{cases}$$
      end
    end
    update count on how many different cells passed in each voxel.
  end
end

The probability of cell migration to each voxel is defined as the ratio of the number of different cells passing through that voxel to the maximum number of different cells passing through any voxel.

The random walk model was implemented in C++ and the probability maps were displayed using Matlab. The simulations were performed on a pentium D 3GHz, linux 2.6.17 workstation. For a simulation with approximately 750-1500 surface voxels, 500 cells in each surface voxel and each walk having 500 steps, the run time was between 2 to 8 minutes.

[1] http://lcni.uoregon.edu/ jolinda/MRIConvert/

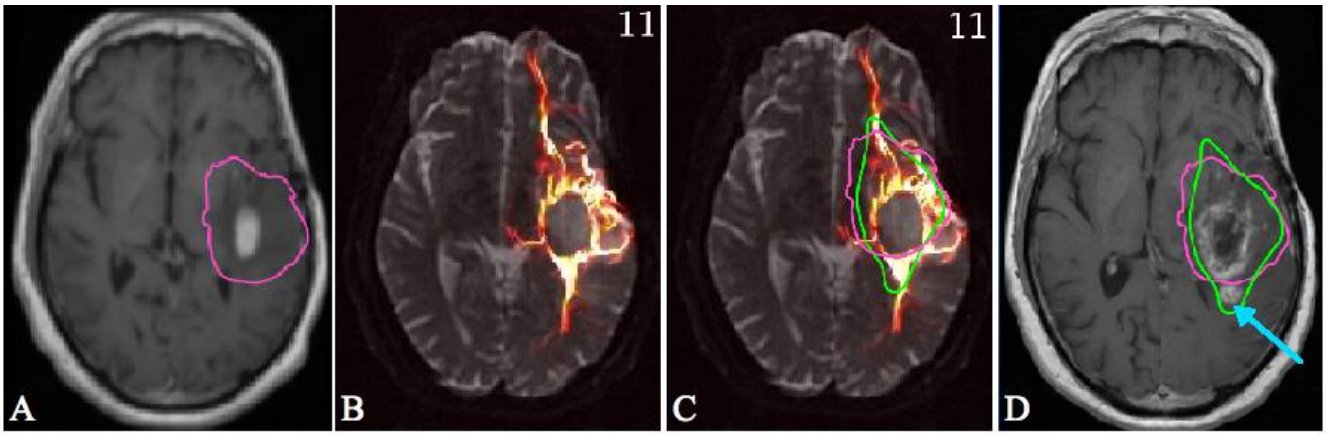

Fig. 1. Depiction of cell migration model results for retrospective case of anaplastic astrocytoma. [A] T1 weighted post-contrast image showing the primary anaplastic astrocytoma and treatment margin (pink line - 90% isodose) obtained from the CT treatment plan. [B] Map of cell concentration showing areas of high concentration in yellow and lower concentration in red. The slice number is shown in top right corner. [C] The treatment plan that was used for SRT (pink line) and the proposed anisotropic treatment plan (green line) designed by increasing the dose along areas of high cell concentration (by 1-2cm) and reducing the dose margin given to the surrounding normal tissue. These plans are depicted on the follow-up T1 weighted post-contrast image [D] showing the location of the secondary tumor (aquamarine arrow) within the proposed anisotropic treatment plan (green line).

3. RESULTS

The random walk model was performed on 4 patient datasets for the retrospective analysis and on 5 patient datasets for the prospective analysis. In all the simulations for retrospective analysis there was a high correlation between the location of secondary tumors and the areas of high cell concentration determined using the model. The result of one of these patients is presented in Fig 1. The patient had an anaplastic astrocytoma in the left temporal lobe (Fig 1A). The 90% isodose volume from the treatment plan is transferred and shown in the images by the pink curve. Fig 1B shows the map of cell concentration. The areas of high concentration in Fig 1B correlate well with the location of the secondary tumor (aquamarine arrow in Fig 1D). Fig 1C illustrates a hypothetical anisotropic treatment plan that was designed by increasing the dose along areas of high cell concentration and reducing the dose margin given to the surrounding normal tissue. Had this new anisotropic treatment plan been applied to this patient, this may have prevented the secondary tumor which indeed did occur posterior to the primary tumor (Fig 1B,1C).

To date, only one of the five patients in the prospective analysis has developed a recurrence (Fig 2). The primary tumor of this patient was a glioblastoma multiforme in the left occipital lobe (Fig 2A). The recurrence was observed 3 months later (aquamarine arrow in Fig 2D) and it was in an area of high cell concentration determined using our model (Fig 2B, 2C). The other patients in the prospective study will have regular follow-up images acquired to monitor recurrence.

4. DISCUSSION

The results support our hypothesis that cell migration from the tumor surface can be modeled by a random walk constrained by the diffusion environment. Thus far, all the patients studied show a high correlation between areas of high cell concentration determined by our model and the location of recurrences and/or secondary tumors.

Our model incorporates two key variables: step size (δ) and the uncertainty in step direction which is bounded by $max\Delta Angle$. $max\Delta Angle$ was selected based on the consideration of the correlation between uncertainty in PDDs and FA. Fig 3 in [9] depicts the standard deviation of PDD with respect to FA for both one-tensor and two-tensor models. To account for potential fiber crossing in our one-tensor analysis, we chose values for $max\Delta Angle$ higher than those for the one-tensor model in [9] but substantially lower than for their two-tensor model.

The random walk of tumor cells was simulated using a varying step-size (δ) based on FA values. The analysis was repeated (data not shown) using constant step-size (δ=$1/4$ $\times$ in-plane resolution). There was no significant difference between the two types of simulations. Even if a smaller step-size was used, the tumor cell is constrained to move approximately in the same direction within the voxel as the PDD in a voxel does not change.

In our random walk model we assume that the initial cell concentration is a step function, that all the surface voxels initially have the same number of tumor cells and that cell migration depends only on the diffusion environment that the

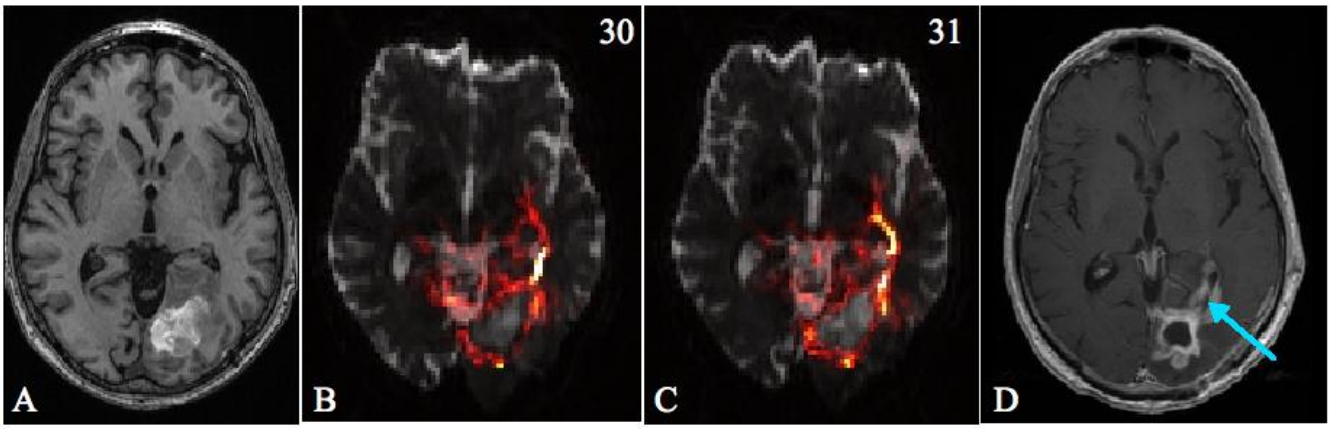

Fig. 2. Depiction of cell migration model results for prospective case of Glioblastoma Multiforme (GBM). [A] T1 weighted post-contrast image showing the primary GBM. [B,C] Map of cell concentration showing areas of high cell concentration in yellow and lower concentration in red. The slice number is shown in top right corner. [D] T1 weighted post-contrast follow up image showing the recurrence (aquamarine arrow) in an area of high cell concentration determined using our model (Figs [B] and [C]).

cell encounters. In the first few steps of each cell, the concentration profile will assume a more realistic distribution based on the diffusion environment. It is known that various factors influence the migration of cells from the tumor surface, therefore further studies are required to determine the relative influence of these factors on cell migration.

5. CONCLUSION

In four out of four retrospective patients and one out of one prospective patients there is a high correlation between areas of high cell concentration determined using the model and the location of recurrences and/or secondary tumors. To verify our hypothesis we are currently acquiring DTI datasets on more patients as part of this prospective study.

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